HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Valturna safely and effectively. See full prescribing information for Valturna.
Valturna (aliskiren and valsartan, USP) Tablets
Initial U.S. Approval: 2009

WARNING: AVOID USE IN PREGNANCY
See full prescribing information for complete boxed warning.

When pregnancy is detected, discontinue Valturna as soon as possible. When used in pregnancy during the second and third trimester, drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)

INDICATIONS AND USAGE

Valturna is a combination of aliskiren, a direct renin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB), indicated for the treatment of hypertension:

- In patients not adequately controlled with monotherapy. (1)
- May be substituted for titrated components. (1)
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. (1)

DOSAGE AND ADMINISTRATION

- Add-on therapy or initial therapy: Initiate with 150/160 mg. Titrate as needed up to a maximum of 300/320 mg. (2.1, 2.3, 2.5)
- Majority of effect attained within 2 weeks. (2.2)
- Replacement therapy: may be substituted for titrated components. (2.4)
- One tablet daily, with a routine pattern with regard to meals. (2.7)

DOSAGE FORMS AND STRENGTHS

Tablets (mg aliskiren/mg valsartan): 150/160, 300/320. (3)

WARNINGS AND PRECAUTIONS

- Avoid fetal or neonatal exposure. (5.1)
- Head and neck angioedema: Discontinue Valturna and monitor until signs and symptoms resolve. (5.2)
- Hypotension in volume- or salt-depleted patients: Correct imbalances before initiating therapy with Valturna. (5.3)
- Patients with renal impairment: Decreases in renal function may be anticipated in susceptible individuals. (5.4)
- Patients with hepatic impairment: Slower clearance may occur. (5.5)
- Hyperkalemia: Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk. (5.7)

ADVERSE REACTIONS

The most common adverse events (incidence ≥1.5% and more common than with placebo) are: Fatigue and nasopharyngitis. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Aliskiren:

- Cyclosporine: Concomitant use is not recommended. (7)

Valsartan:

- Potassium sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium, and in heart failure patients, increases in serum creatinine. (7)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: Nursing or drug should be discontinued. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2010

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: AVOID USE IN PREGNANCY

When pregnancy is detected, discontinue Valturna as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus. *[See Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Valturna is indicated for the treatment of hypertension.

Add-on Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with Valturna.

Replacement Therapy

Valturna may be substituted for the titrated components.

Initial Therapy

Valturna may be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of Valturna as initial therapy should be based on an assessment of potential benefits and risks.

Patients with Stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study *[see Clinical Studies (14)]* provide estimates of the probability of reaching a target blood pressure with Valturna compared to aliskiren or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Valturna 300/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of a small number of subjects with high baseline blood pressures.

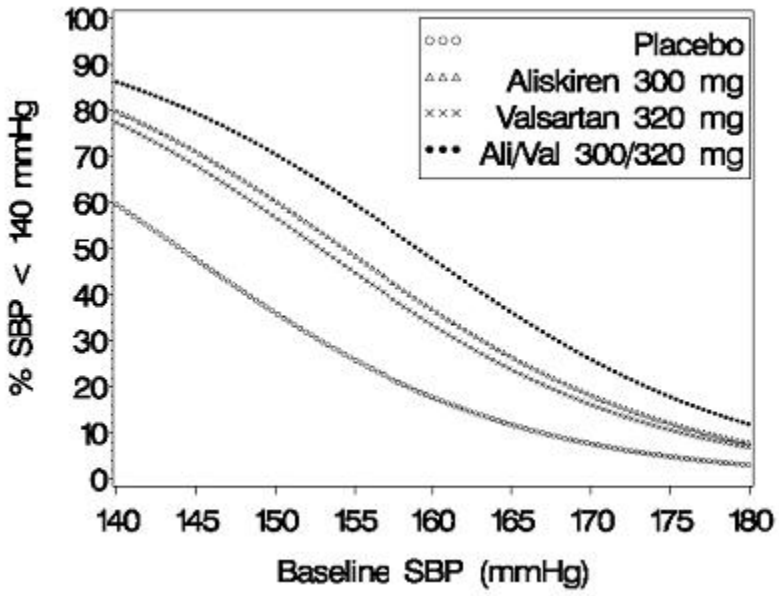


Figure 1: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg in Patients at Endpoint

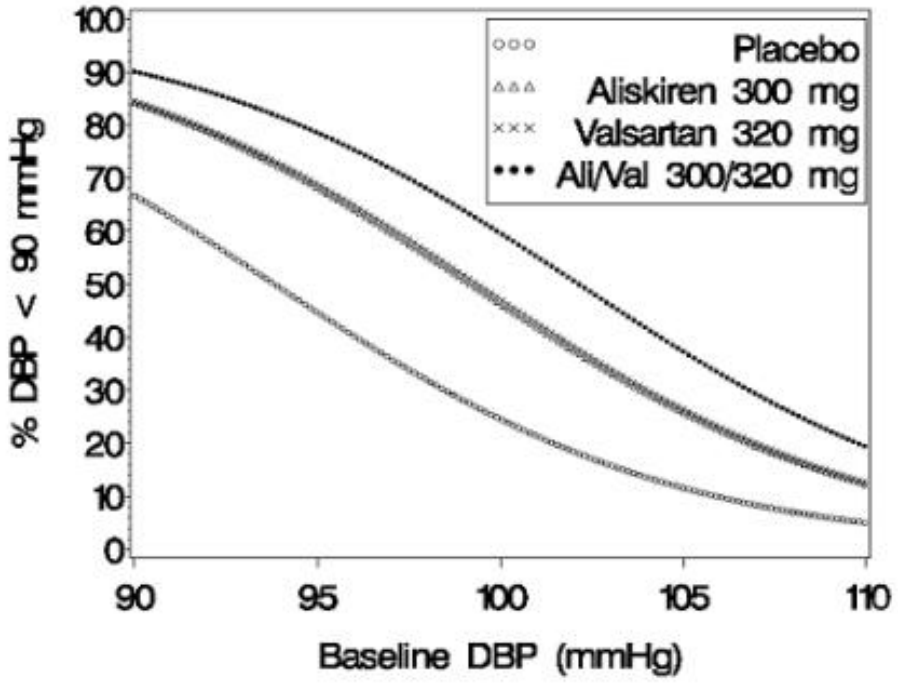


Figure 2: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in Patients at Endpoint

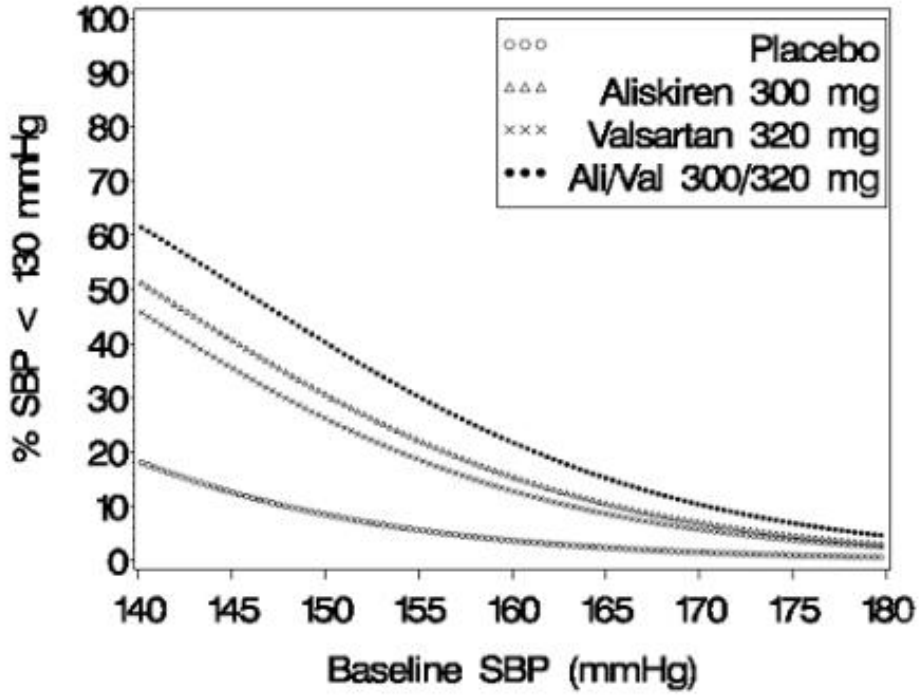


Figure 3: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in Patients at Endpoint

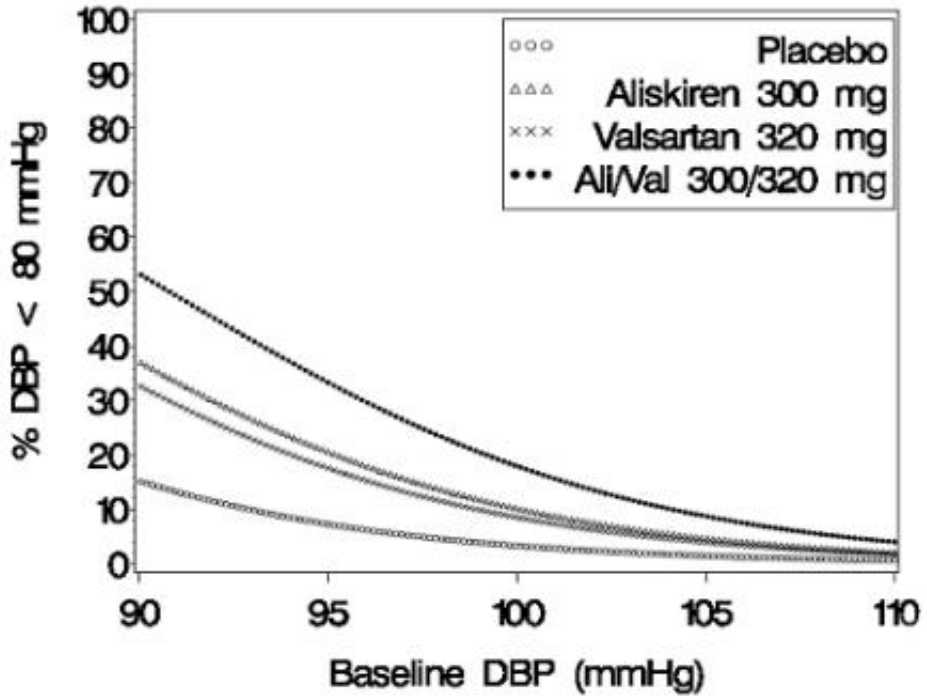


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in Patients at Endpoint

At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy. For example, the mean baseline SBP/DBP for patients participating in this multifactorial study was 154/100 mmHg. A patient with a baseline blood pressure of 154/100 mmHg has about a 51% likelihood of achieving a goal of <140 mmHg (systolic) and 46% likelihood of achieving <90 mmHg (diastolic) on aliskiren alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) and 47% (diastolic). The likelihood of achieving these goals on Valturna rises to about 62% (systolic) and 60% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) and 25% (diastolic) *[see Dosage and Administration (2) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dose Selection

The recommended once-daily dose of Valturna is 150/160 mg or 300/320 mg. The recommended initial once-daily dose of Valturna is 150/160 mg. Titrate as needed to a maximum of 300/320 mg.
Patients switched from monotherapy to Valturna on average experience greater blood pressure reductions with use of the combination product.

2.2 Dose Titration

The antihypertensive effect of Valturna is largely attained within 2 weeks. If blood pressure remains uncontrolled after 2 to 4 weeks of therapy, the dose may be titrated up to a maximum of 300/320 mg.

2.3 Add-on Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with Valturna. The usual recommended starting dose is 150/160 mg once daily as needed to control blood pressure.

2.4 Replacement Therapy

For convenience, patients receiving aliskiren and valsartan from separate tablets may instead wish to receive a single tablet of Valturna containing the same component doses.

2.5 Initial Therapy

The usual recommended starting dose of Valturna is 150/160 mg once daily as needed to control blood pressure. The dose may be titrated up to a maximum of 300/320 mg once daily.
Valturna is not recommended for use as initial therapy in patients with intravascular volume depletion *[see Warnings and Precautions (5.3)]*.

2.6 Use with Other Antihypertensive Drugs
Valturna may be administered with other antihypertensive agents. There are no data available with use of Valturna with angiotensin-converting enzyme inhibitors or other renin-angiotensin-aldosterone blockers.

2.7 Relationship to Meals
Patients should establish a routine pattern for taking Valturna with regard to meals. High-fat meals decrease absorption substantially *[see Clinical Pharmacology (12.3)]*.

2.8 Dosing in Specific Populations
Renal Impairment
Adjustment of the starting dose is not required in patients with mild-to-moderate renal impairment. Clinical experience with dosing Valturna in patients with moderate renal impairment is limited. No data are available in patients with severe renal impairment *[see Warnings and Precautions (5.4)]*.
Hepatic Impairment
Adjustment of the starting dose is not necessary with mild or moderate hepatic impairment. Clinical experience with dosing Valturna in patients with severe hepatic impairment is limited *[see Warnings and Precautions (5.5)]*.
Elderly Patients
Adjustment of the starting dose is not required for elderly patients.

3 DOSAGE FORMS AND STRENGTHS
- 150/160 mg aliskiren/valsartan tablets: light red, standard convex ovaloid, film-coated tablets with beveled edges debossed with NVR/HDU

- 300/320 mg aliskiren/valsartan tablets: light brown, shallow convex ovaloid, film-coated tablets with beveled edges debossed with NVR/SNB

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality
Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.
Drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*. In several dozen published cases, use of ACE inhibitors during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in retrospective data.

5.2 Head and Neck Angioedema
Aliskiren
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patent airway may be necessary.
Discontinue aliskiren immediately in patients who develop angioedema and do not readminister.

5.3 Hypotension
An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valturna in controlled trials.
In patients with an activated renin-angiotensin-aldosterone system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to the administration of Valturna, or start the treatment under close medical supervision.
Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing

instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.
If an excessive fall in blood pressure occurs with Valturna, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.4 Patients with Severe Renal Impairment

Valturna

Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.

Aliskiren

Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.

Valsartan

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

5.5 Patients with Hepatic Impairment

Valsartan

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs).

5.6 Patients with Congestive Heart Failure and Post-Myocardial Infarction

Valsartan

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction.

5.7 Serum Electrolyte Abnormalities

Valturna

In the short-term controlled trials of various doses of Valturna, the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo. In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.
Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.
Caution is advised with concomitant use of Valturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.

5.8 Renal Artery Stenosis

Aliskiren

No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Valsartan
In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

5.9 Cyclosporine
Aliskiren
When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Risk of fetal/neonatal morbidity and mortality *[see Warnings and Precautions (5.1)]*
- Head and neck angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.
Valturna
Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valturna versus 2.7% of patients given placebo.
Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs. 0.3%).
Hyperkalemia has been observed as a serum electrolyte abnormality in Valturna clinical trials *[see Warnings and Precautions (5.7)]*.
Aliskiren
Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.
Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.
In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.
In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.
Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.
Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.
Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).
Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.
No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.
Valsartan
Valsartan has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials, including over 400 treated for over 6 months, and more than 160 for over 1 year.
In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p<0.001$).
Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:
Body as a Whole: allergic reaction, asthenia
Musculoskeletal: muscle cramps
Neurologic and Psychiatric: paresthesia
Respiratory: sinusitis, pharyngitis
Urogenital*:* impotence
Other reported events seen less frequently in clinical trials were: angioedema.
Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

6.2 Clinical Laboratory Test Abnormalities
RBC count, hemoglobin and hematocrit:
Small mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but changes in hemoglobin were slightly more pronounced with the combination therapy (-0.26 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (+0.07 g/dL).
Blood Urea Nitrogen (BUN)/Creatinine:
Elevations in BUN (>40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of the study and a 30% increase from baseline compared to none in either monotherapy or placebo.
Serum Electrolytes: See Warnings and Precautions (5.7)

6.3 Post-Marketing Experience
The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Hypersensitivity: angioedema requiring airway management and hospitalization
Peripheral edema

7 DRUG INTERACTIONS
No drug interaction studies have been conducted with Valturna and other drugs, although studies with the individual aliskiren and valsartan components are described below.
Aliskiren
Effects of Other Drugs on Aliskiren
Based on in vitro studies, aliskiren is metabolized by CYP 3A4.
Irbesartan: Coadministration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.
P-glycoprotein Effects: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.
Atorvastatin: Coadministration of atorvastatin, a weak Pgp inhibotor, resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.
Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a moderate Pgp inhibitor, with aliskiren resulted in approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.
Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine, a potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5-fold increase in C_{max} and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.

Verapamil: Coadministration of 240 mg of verapamil, a moderate Pgp inhibitor, with 300 mg aliskiren resulted in an approximately 2-fold increase in C_{max} and AUC of aliskiren. However, no dosage adjustment is necessary.
Drugs with no clinically significant effects: Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.
Effects of Aliskiren on Other Drugs
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.
Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.
Drugs with no clinically significant effects: Coadministration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.
Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with aliskiren, amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.
Warfarin: Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.
CYP 450 Interactions: *In vitro* metabolism studies have indicated that CYP450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of low extent of metabolism (*see Pharmacokinetics – Valsartan (12.3*).
Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.1)]*.
Valturna contains both aliskiren (a direct renin inhibitor) and valsartan (an angiotensin II receptor blocker). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death. Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.
Angiotensin II receptor antagonists, like valsartan, and angiotensin-converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin-aldosterone system, has been associated with a potential risk of birth defects in retrospective data.
When pregnancy occurs in a patient using Valturna, discontinue Valturna treatment as soon as possible. Inform the patient about potential risks to the fetus based on the time of gestational exposure to Valturna (first trimester only or later). If exposure occurs beyond the first trimester, perform an ultrasound examination.
In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, perform serial ultrasound examinations to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Valturna treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Closely observe infants with histories of *in utero* exposure to Valturna for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension or support decreased renal function.
No reproductive toxicity studies have been conducted with the combination of aliskiren and valsartan. However, these studies have been conducted for aliskiren as well as valsartan alone *[see Nonclinical Toxicology (13)]*.

8.3 Nursing Mothers

It is not known whether aliskiren is excreted in human milk, but aliskiren was secreted in the milk of lactating rats. It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Valturna in pediatric patients have not been established.

8.5 Geriatric Use

In the short-term controlled clinical trials of Valturna, 99 (15.9%) patients treated with Valturna were ≥65 years and 14 (2.2%) were ≥75 years.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Aliskiren

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan is not removed from the plasma by hemodialysis.

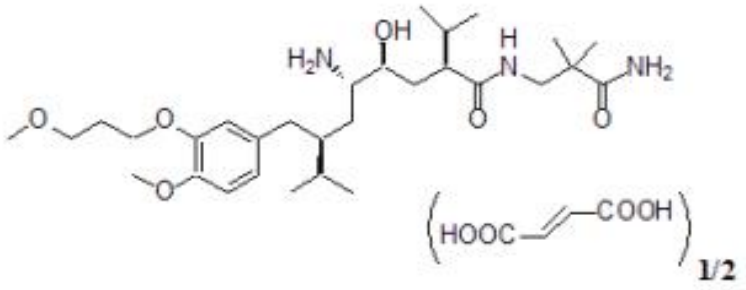
Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11 DESCRIPTION

Valturna is a single tablet of aliskiren (an orally active, nonpeptide, potent direct renin inhibitor) and valsartan (an orally active, nonpeptide, specific angiotensin II antagonist acting on the AT_1 receptor subtype).

Aliskiren

Aliskiren hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is

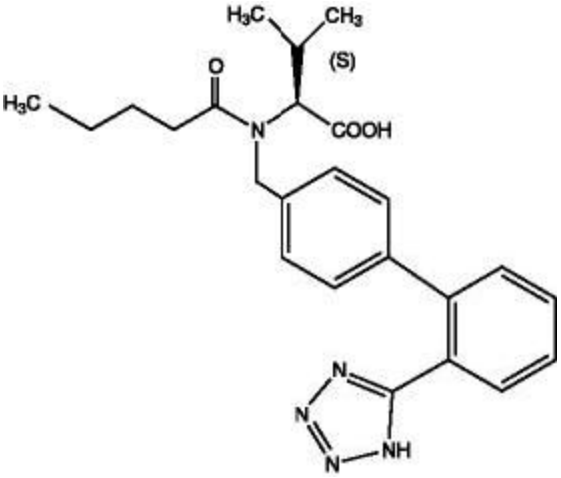


Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$

Aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). It is soluble in phosphate buffer, n-octanol, and highly soluble in water.

Valsartan

Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine; its structural formula is



Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5.

Valturna tablets are formulated for oral administration to contain aliskiren hemifumarate and valsartan, USP 150/160 mg, and 300/320 mg. The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, indigotin blue lake, iron oxide black, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide and hypromellose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aliskiren

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

Valsartan

Ang II is formed from Ang I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Ang II is the principal pressor agent of the renin-angiotensin-aldosterone system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of Ang II by selectively blocking the binding of Ang II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for Ang II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin-aldosterone system with ACE inhibitors, which inhibit the biosynthesis of Ang II from Ang I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the Ang II receptor inhibits the negative regulatory feedback of Ang II on renin secretion, but the resulting increased PRA and Ang II circulating levels do not overcome the effect of valsartan on blood pressure.

Valsartan has indications other than hypertension which can be found in the Diovan® package insert.

Valturna

Since aliskiren and valsartan block the RAAS at different sites (inhibition of plasma renin activity and antagonism of the AT_1 receptor), their combination provides a complementary mechanism to achieve a pharmacologic inhibition of the RAAS. Such RAAS inhibition with Valturna is associated with significant reductions in PRA, Ang I, Ang II and aldosterone.

12.2 Pharmacodynamics

Aliskiren

PRA reductions in clinical trials ranged from approximately 50% to 80%, were not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

Valsartan

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.

Valturna

In normotensive subjects receiving sodium supplementation, a single oral dose of 320 mg valsartan increased PRA, angiotensin I and angiotensin II, whereas 300 mg of aliskiren decreased them for 48 hours. In combination, 150 mg of aliskiren neutralized the 160 mg valsartan-induced increase in PRA, plasma angiotensin I and angiotensin II for 48 hours. The reduction in urinary aldosterone excretion with the 150/160 mg aliskiren/valsartan combination was similar to 300 mg of aliskiren and greater than that of 320 mg of valsartan and placebo.

12.3 Pharmacokinetics

Absorption and Distribution

Valturna

Following oral administration of Valturna combination tablets, the median peak plasma concentration times are within 1 hour for aliskiren and 3 hours for valsartan. The mean half-lives of aliskiren and valsartan are 34 hours and 12 hours, respectively. The rate and extent of absorption of aliskiren and valsartan from Valturna are the same as when administered as individual tablets. When taken with food, mean AUC and C_{max} of aliskiren are decreased by 76% and 88%, respectively; mean AUC and C_{max} of valsartan were not significantly affected. In clinical trials of Valturna, it was administered without requiring a fixed relation of administration to meals.

Valsartan

The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Metabolism and Elimination

Aliskiren

About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the *in vitro* studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4.

Valsartan

Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. *In vitro* metabolism studies involving recombinant CYP450 enzymes indicated that the CYP2C9 isozyme is responsible for the formation of valeryl-4-hydroxy valsartan. It has also been shown that valsartan does not inhibit CYP450 isozymes at clinically relevant concentrations. CYP450 mediated drug interactions between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Special Populations

Pediatric Patients

The pharmacokinetics of Valturna have not been investigated in patients <18 years of age.

Geriatric Patients

The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients. Adjustment of the starting dose is not required in these patients. Exposure (measured by AUC) to valsartan is higher by 70%

and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary *[see Dosage and Administration (2.8)]*.

Race

With Valturna, pharmacokinetic differences due to race have not been studied. The pharmacokinetic differences among Blacks, Caucasians, and Japanese are minimal with aliskiren therapy.

Renal Impairment

Aliskiren

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal impairment. Rate and extent of exposure (AUC and C_{max}) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients *[see Dosage and Administration (2.8)]*.

Valsartan

There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis *[see Dosage and Administration (2.8)]*.

Hepatic Impairment

Aliskiren

The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to-severe liver disease. Consequently, adjustment of the starting dose is not required in these patients *[see Dosage and Administration (2.8)]*.

Valsartan

On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease *[see Dosage and Administration (2.8)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Valturna

No carcinogenicity, mutagenicity or fertility studies have been conducted for Valturna alone as these studies have been conducted for each individual component. Valturna has been studied in 2- and 13-week toxicity studies and was generally well-tolerated. Findings were primarily attributable to the exaggerated pharmacological effects of each component.

Aliskiren

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure ($AUC_{0\text{-}24hr}$) basis, 1500 mg/kg/day in the rat is about 4 times and in the mouse about 1.5 times the maximum recommended human dose (300 mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.

Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, the *in vitro* Chinese hamster V79 cell gene mutation test and the *in vivo* mouse bone marrow micronucleus assay.

Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Tekturna/60 kg on a mg/m^2 basis).

Valsartan

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m^2 basis. (Calculations based on a 60 kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Aliskiren

Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose [MRHD] of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected

in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up at 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

14 CLINICAL STUDIES

Valturna

Aliskiren 150 mg and 300 mg and valsartan 160 mg and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 mg and 160 mg, respectively, and increased at four weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were statistically significantly ($p<0.05$) greater than the reductions with the monotherapies as shown in Table 1.

Table 1: Reductions in Seated Trough Cuff Blood Pressure of Aliskiren in Combination with Valsartan

		Valsartan, mg		
Aliskiren, mg	(mmHg)	0	160	320
0	Mean Change	4.6/4.1*	10.9/8.7	12.8/9.7
	Placebo-Subtracted Mean Change	--	5.6/3.9[p]	8.2/5.6[p]
150	Mean Change	10.7/7.5	15.3/10.5	--
	Placebo-Subtracted Mean Change	5.4/2.7[p]	10.0/5.7[pav]	--
300	Mean Change	13.0/9.0	--	17.2/12.2
	Placebo-Subtracted Mean Change	8.4/4.9[p]	--	12.6/8.1[pav]

* The placebo change is 5.2/4.8 for Week 4 endpoint which was used for the dose groups containing aliskiren 150 mg or valsartan 160 mg.

[p] $p<0.05$ vs. placebo by ANCOVA for the pairwise comparison.

[a] $p<0.05$ vs. respective aliskiren monotherapy by ANCOVA for the pairwise comparison.

[v] $p<0.05$ vs. respective valsartan monotherapy by ANCOVA for the pairwise comparison.

The safety and efficacy of Valturna as initial therapy were evaluated. The figures *[see Indications and Usage (1)]* display the probability that a patient will achieve systolic or diastolic blood pressure goal with Valturna 300/320 mg, based upon their baseline systolic or diastolic blood pressure. At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy.

The antihypertensive effect of Valturna was attained within 2 weeks.

One active-controlled trial investigated the addition of aliskiren 300 mg plus valsartan 320 mg in hypertensive patients who did not respond adequately to HCTZ 25 mg, and showed decreases from baseline in systolic and diastolic blood pressure of approximately 22/16 mmHg compared with approximately 6/6 mmHg with continuation of HCTZ 25 mg alone.

The antihypertensive effect was similar in patients with or without diabetes, in patients ≥65 years of age and <65 years of age, and in women and men. The effects of aliskiren, valsartan, and the combination were diminished in Blacks compared to Caucasians as has been seen with ACE inhibitors, other angiotensin receptor blockers, and beta blockers.

16 HOW SUPPLIED/STORAGE AND HANDLING

Valturna is supplied as convex, beveled edged, ovaloid film-coated tablets.

All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below.

Table 2: Valturna Tablets Supply

Tablet	Color	Debossed	Debossed	NDC 0078-XXXX-XX		
Aliskiren/valsartan		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg/160 mg	Light Red	NVR	HDU	0572-15	0572-34	0572-35

300 mg/320 mg	Light Brown	NVR	SNB	0574-15	0574-34	0574-35

Storage
Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) in original container. [See USP Controlled Room Temperature.]
Protect from moisture.
Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION
Healthcare professionals should instruct their patients to read the Patient Package Insert before starting Valturna and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.
Pregnancy
Tell female patients of childbearing age about the consequences of exposure to drugs that act on the renin-angiotensin-aldosterone system. Discuss other treatment options with female patients planning to become pregnant. Ask these patients to report pregnancies to their physicians as soon as possible.
Symptomatic Hypotension
Caution patients receiving Valturna that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. Tell the patients that if syncope occurs, discontinue Valturna until the physician has been consulted.
Caution all patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.
Potassium Supplements
Tell patients receiving Valturna not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.
Relationship to Meals
Patients should establish a routine pattern for taking Valturna with regard to meals. High-fat meals decrease absorption substantially.

FDA-Approved Patient Labeling
Patient Information

Valturna® (val-tur-na)
(aliskiren and valsartan, USP) Tablets
Read the Patient Information that comes with Valturna before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition and treatment.
IMPORTANT WARNING: Valturna may harm an unborn baby, causing injury and death. If you get pregnant, stop taking Valturna and call your doctor right away. If you plan to become pregnant, talk to your doctor about other medicines to treat your high blood pressure before taking Valturna.
What is Valturna?
Valturna contains two prescription medicines in one tablet that work together to lower blood pressure. It contains:
• aliskiren (Tekturna), a direct renin inhibitor (DRI)

• valsartan (Diovan), an angiotensin receptor blocker (ARB)

Aliskiren (Tekturna) reduces the effect of renin, and the harmful process that narrows blood vessels. Aliskiren also helps blood vessels relax and widen so blood pressure is lower. Valsartan (Diovan) can help lower your blood pressure by blocking a potent chemical, angiotensin II, that leads to blood vessel constriction and narrowing.
Valturna may be used to lower high blood pressure in adults:
• when one medicine to lower high blood pressure is not enough

• as the first medicine to lower high blood pressure if your doctor decides that you are likely to need more than one medicine

Valturna has not been studied in children under 18 years of age.
Your doctor may prescribe other medicines for you to take along with Valturna to treat your high blood pressure.
What is high blood pressure (hypertension)?
Blood pressure is the force that pushes the blood through your blood vessels to all the organs of your body. You have high blood pressure when the force of your blood moving through your blood vessels is too great. One cause of high blood pressure is renin, a chemical in the body that starts a process that makes blood vessels narrow, leading to high blood pressure.
Valturna reduces high blood pressure. Medicines that lower your blood pressure lower your chance of having a stroke or heart attack. High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.
Blood pressure is reduced more with Valturna than when either Tekturna or Diovan is taken by itself.

Who should not take Valturna?

- **If you get pregnant, stop taking Valturna and call your doctor right away. If you plan to become pregnant, talk to your doctor about other treatment options for your high blood pressure.**

- **Do not take Valturna if you are allergic to any of its ingredients. See the end of this leaflet for a complete list of the ingredients in Valturna.**

What should I tell my doctor before taking Valturna?

Tell your doctor about all your medical conditions, including whether you:

- have kidney problems

- have liver problems

- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue, throat, arms and legs, and may cause difficulty breathing.

- are pregnant or planning to become pregnant. See IMPORTANT WARNING.

- are breast-feeding**.** It is not known if Valturna passes into your breast milk.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you are taking:

- other medicines for high blood pressure or a heart problem

- water pills (also called “diuretics”)

- medicines for treating fungus or fungal infections

- cyclosporine (a medicine used to suppress the immune system)

- potassium-containing medicines, potassium supplements, or salt substitutes containing potassium

- atorvastatin

Your doctor or pharmacist will know what medicines are safe to take together. Know your medicines. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine.

How should I take Valturna?

- Take Valturna exactly as prescribed by your doctor. It is important to take Valturna every day to control your blood pressure.

- Take Valturna once each day, about the same time each day.

- Take Valturna the same way everyday, either with or without a meal.

- Your doctor may change your dose of Valturna if needed.

- If you miss a dose of Valturna, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time.

- If you take too much Valturna, call your doctor or a Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of Valturna?

Valturna may cause serious side effects:

- **Injury or death to an unborn baby.** See IMPORTANT WARNING.

- **Low blood pressure (hypotension).** Your blood pressure may get too low if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Drinking alcohol and taking certain medicines (barbiturates or narcotics) can cause low blood pressure to get worse. Lie down if you feel faint or dizzy, and call your doctor right away.

- **Angioedema.** Aliskiren, a component in Valturna, can cause swelling of the face, lips, tongue, throat, arms and legs, or the whole body. Get medical help right away and tell your doctor if you get any one or more of these symptoms. Angioedema can happen at any time while you are taking Valturna.

Common side effects of Valturna include:

- Tiredness
- Sore throat
- Runny nose
- Diarrhea
- Upper respiratory tract infection
- Urinary tract infection
- Flu or flu-like symptoms
- Dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Valturna. For a complete list of side effects, ask your doctor or pharmacist.

How do I store Valturna?

- Store Valturna tablets at room temperature between 59^{o}F-86^{o}F (15^{o}C-30^{o}C).
- Keep Valturna in the original prescription bottle in a dry place. Do not remove the desiccant (drying agent) from the bottle.

Keep Valturna and all medicines out of the reach of children.

General information about Valturna

Medicines are sometimes prescribed for conditions not listed in the patient information leaflet. Do not take Valturna for a condition for which it was not prescribed. Do not give Valturna to other people, even if they have the same condition or symptoms you have. It may harm them.

This leaflet summarizes the most important information about Valturna. If you have questions about Valturna talk with your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

For more information about Valturna, visit www.valturna.com or call 1-877-282-5887.

What are the ingredients in Valturna?

Active ingredients: Aliskiren and valsartan

Inactive ingredients: The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, indigotin blue lake, iron oxide black, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide, and hypromellose

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
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PRINCIPAL DISPLAY PANEL

Package Label – 150 mg/160 mg

Rx Only NDC 0078-0572-15
Valturna® (aliskiren and valsartan) Tablets
150 mg aliskiren and
160 mg valsartan per tablet
30 Tablets

PRINCIPAL DISPLAY PANEL
Package Label – 300 mg/320 mg
Rx Only NDC 0078-0574-15
Valturna® (aliskiren and valsartan) Tablets
300 mg aliskiren and
320 mg valsartan per tablet
30 Tablets

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